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Original Article

Management of dermatologic adverse events associated with tumor treating fields in patients with glioblastoma multiforme: A 27-case series

Xiaoxue Chen [1], Yihong Zhang [1], Qinqin Zhao, Lan Bai, Xiaoqun Chen, Zhihuan Zhou [*]

Department of Neurosurgery/Neuro-Oncology, State Key Laboratory of Oncology in South China, Collaborative Innovation Center for Cancer Medicine, Sun Yat-sen University Cancer Center, Guangzhou, China

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ABSTRACT

Objective: This study summarized the clinical management of 27 patients with glioblastoma multiforme who tumor treating fields therapy for the healthcare providers.
Methods: Glioblastoma multiforme patients who experienced dermatologic adverse events after tumor treating fields therapy from April 2019 to May 2021 were included. The clinical management involved educating patients and their caregivers on the prevention of dermatologic adverse events, scalp assessment and preparation, and removal and replacement of the transducer array. Informed consent for participating in the study including the taking of pictures was obtained from all patients.
Results: The dermatologic adverse events were successfully managed in all 27 patients, with no severe dermatologic adverse events were reported.
Conclusions: Data on tumor treating fields-related dermatologic adverse events is rarely reported, and published reports of management of scalp dermatologic adverse events are lacking. This case series summarizes a clinically individualized management for tumor treating fields-related dermatologic adverse events.

Introduction

Glioblastoma multiforme (GBM) is the most common and lethal diffuse type of neuroglioma, accounting for 45.2% of malignant primary brain and central nerve system (CNS) tumors.[1,2] The standard-of-care multimodality therapy for patients with newly diagnosed GBM includes maximal safe surgical resection and concurrent chemoradiation with temozolomide followed by maintenance temozolomide, which is associated with a median overall survival (OS) of 19 months.[3,4]

Maximum surgical resection or radiotherapy with concomitant temozolomide chemotherapy is effective in newly diagnosed cases of GBM but does not eradicate infiltrating tumor cells, with tumor progression and recurrence being common.[5] Bevacizumab combined with chemotherapy was shown to improve 6-month progression-free survival (PFS) rates and was approved by the United States Food and Drug Administration for the treatment of patients with recurrent GBM, but did not improve patients' health-related quality of life (HRQoL) or neurocognitive function.[6]

Tumor treating fields (TTFields) therapy is a novel, non-invasive treatment involving the locoregional delivery of low-intensity alternating electric fields (200 kHz) via a non-invasive transducer array to selectively interfere with GBM cell division without damaging non-mitotically active cells. The electric fields are not attenuated by increased array spacing, do not have a half-life as in the case of drugs, can reach deep GBM tumors.[7–10] In the phase 3 prospective multi-center EF-11 trial, PFS and mean OS rates of patients with recurrent GBM receiving TTFields therapy were increased (although not significantly) compared to the chemotherapy-treated control group.[10] In a recent multi-center, open-label randomized phase 3 trial (EF-14), TTFields therapy combined with temozolomide increased median PFS by 2.7 months and median OS by 4.9 months and improved HRQoL compared to standard maintenance temozolomide chemotherapy in patients with newly diagnosed GBM.[11] Based on its efficacy and safety, TTFields therapy was approved by the Food and Drug Administration for the treatment of recurrent GBM in 2011 and for newly diagnosed GBM in 2015 and was approved for these indications in China in 2020.

The efficacy of TTFields therapy in GBM is strongly correlated with treatment duration, with guidelines recommending a minimum of 18 h of uninterrupted exposure to the electric field. However, this can lead to dermatologic adverse events (dAEs) including contact dermatitis,

* Corresponding author.
E-mail address: zhouzhh@sysucc.org.cn (Z. Zhou).
[1] These authors have contributed equally to this work as joint first author.

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hyperhidrosis, xerosis or pruritus, skin erosion and ulceration, and skin and soft tissue infection (SSTI).[12] According to the literature, 5.3%–13.8% of patients with GBM treated with temozolomide chemotherapy experience dAEs, and radiotherapy, as a means of traumatic treatment, also has consequences on the systemic skin and mucosa.[13,14] The dAEs of radiotherapy with concomitant temozolomide chemotherapy may be superimposed. TTFields therapy is frequently implemented in combination with chemotherapy and radiation, which may further heighten the risk of dAEs.[15] It was reported that 16% of patients with GBM and treated with TTFields therapy in the EF-11 trial and 52% who received TTFields therapy in combination with temozolomide experienced mild to moderate (grade 1 and 2) contact dermatitis and skin irritation, respectively.[10,11] It is also recommended that patients with GBM replace the transducer array and shave the scalp every 3–4 days, which reduces scalp surface resistance.[16] Long-term wear, device removal, and frequent shaving have been identified as the primary causes of dAEs associated with TTFields therapy.[17] These can be divided into four categories according to the Common Terminology Criteria for Adverse Events (CTCAE) of the National Cancer Institute, but this classification does not allow adequate grading of dAEs severity.

Given that dAEs can lead to treatment interruption or discontinuation, it is important to prevent their occurrence in order to improve adherence to TTFields therapy among patients with GBM and thereby improve their prognosis.[12] Therapeutic measures for TTFields-related dAEs in patients with GBM (eg. topical antibiotics, skin barrier film, and topical antiperspirants) depend on the severity and type of the clinical manifestations.[15,18] However, the effectiveness of therapeutic measures in the Chinese population cannot be verified due to the lacking research on the clinical management of TTFields-related dAEs worldwide, especially in China.

This case series describes the clinical management of dAEs in patients with GBM and treated with TTFields therapy at our center, with the aim of providing guidance for healthcare providers to develop an individualized strategy for each patient. To more accurately capture their clinical characteristics, dAEs were graded from 1 (asymptomatic/mild) to 4 (life-threatening) according to a modified version of CTCAE (Table 1).[19,20]

Methods

In this case series, we included all records of 27 patients with newly diagnosed (16/27 [59.3%]) or recurrent (11/27 [40.7%]) GBM who were treated with TTFields therapy for at least 1 month at the Department of Neurosurgery and Radiotherapy, Sun Yat-sen University State Key Laboratory of Oncology in South China (Guangzhou, China) from April 2019 to May 2021. The patients ranged in age from 21 to 66 years, and most were male (18/27 [66.7%]).

All patients underwent TTFields therapy using an Optune kit (Novocure, Saint Helier, Jersey) according to the manufacturer's instructions, with low-intensity (1–3 V/cm) and intermediate-frequency (200 kHz) alternating electric fields in two perpendicular directions applied to the scalp. Two pairs of transducer arrays were worn continuously for a minimum of 18 h for at least 3 days but not more than 4 days, with 2–3 short breaks allowed per week. The hygiene, sterilization, and optimal shaving of the scalp and regular repositioning of the two pairs of transducer arrays before and after TTFields therapy initiation are critical.[16] Appropriate follow-up plans were developed for regular scalp assessment by patients with GBM and their caregivers, and just-in-time, recommendations were provided via different communication channels (i.e. telephone and direct mail).

Before TTFields therapy, all patients with GBM and caregivers were informed by healthcare providers on the necessary precautions when removing and replacing the transducer array. It was recommended that hair on the scalp can be carefully shaved with an electric razor to avoid wounding the skin and ensure good array-to-scalp contact. All patients were instructed to clean the scalp and remove surface sebum and sweat with a mild fragrance-free or anti-seborrheic dermatitis shampoo. The use of 70% isopropyl alcohol or ethanol as disinfectant was not recommended before the placement of the transducer array in patients with oily scalp in order to reduce the risk of scalp irritation and patch displacement. The sterilized TTFields transducer arrays for preventing infections are individually packaged and are for single use (disposable). Prior to attaching the transducer array, the healthcare providers or caregivers used 0.5% povidone iodine (Anerdian; LikangDisinfection Co., Shanghai, China) to sterilize the scalp and then washed the scalp area with soap. The array was attached to the unscarred intact skin while avoiding tension in the wires. No craniotomy closure hardware was used to ensure good contact between the transducer array and scalp.

Transducer arrays should be replaced every 3–4 days to avoid frequent manipulations that could lead to inadvertent damage to the scalp while also avoiding excessive hair ingrowth or hyperhidrosis. The transducer array was carefully removed with mineral oil and shifted 2 cm from the previous position while avoiding the surgical scars and craniotomy hardware. All the methods were performed in accordance with the relevant regulations. Informed consents for participating in the study including the taking of pictures were obtained from all patients. Photographs of the scalp were taken at each removal for documentation purposes. When symptoms were observed, patients were able to provide feedback online through the nursing team' consulting services and seek appropriate advice on how they could be managed.

Case presentation

Eight patients had hyperhidrosis that led to the displacement or loosening of the transducer array. A total of 13 patients presented with pruritus from day 1 up to 4 weeks along with other symptoms—such as erythema, rash, and blistering—sometimes co-occurring. A 4.0 × 10.0 mm (length × width) area of moist and ruddy ulceration with white exudate appeared on the surface of one patient's scalp. In one patient, folliculitis appeared on day 4 followed by desquamation and rash 12 days later. One month later, the patient had a red and swollen herpes lesion 0.5 cm in diameter with a small amount of purulent secretion. Four patients showed cutaneous manifestations including xerosis, pruritus, and increased dandruff; four other patients had xerosis and pruritus with increased dandruff. The detailed clinical and general characteristics, clinical presentation, and dAEs of the 27 cases are summarized in Table 2.

Case 1 – Hyperhidrosis

Immediate replacement of the transducer array was recommended for two patients who experienced melting of the hydrogel. Aluminum chloride antiperspirant or glycopyrrolate ointment smeared on the array is the most effective topical medication for inhibiting sweat secretion.[12]

Table 1
Modified version of Common Terminology Criteria for Adverse Events.

		Grade			
Adverse event	Short name	1	2	3	4
TTFields-related dermatologic adverse event	TTFields-related dAE	Asymptomatic or mild symptoms, topical treatment indicated	Moderate symptoms, topical and systematic treatment indicated	Severe but not life-threatening symptoms, responsive to topical and systematic treatment	Life-threatening symptoms, urgent intervention and device interruption indicated

dAE, dermatologic adverse event; TTFields, tumor treating field.

Table 2
Clinical and general characteristics, clinical presentation, and TTFields-related dermatologic adverse events of the 27 patients in this case series.

Patient No.	Gender	Age, years	Diagnostic status[a]	Hyperhidrosis	Skin rash	Skin erosions and skin ulcers	Skin and soft tissue infections	Xerosis or pruritus	CTCAE grade
1	M	49	1	1	0	0	0	0	1
2	F	29	1	0	1	0	0	1	1
3	M	63	1	0	1	1	0	0	2
4	M	58	0	1	0	0	0	0	0
5	M	61	1	1	1	0	0	0	2
6	F	70	1	1	0	0	0	0	1
7	F	26	1	0	1	0	0	0	1
8	F	23	1	1	0	0	0	0	0
9	M	42	1	0	1	0	0	0	1
10	F	63	1	0	0	0	0	0	0
11	M	53	1	0	1	0	0	0	1
12	M	39	0	0	0	0	0	0	0
13	M	63	1	0	1	0	0	0	1
15	M	47	1	0	0	0	0	0	0
16	M	57	0	0	1	0	0	0	1
17	M	64	1	1	0	1	0	0	1
18	M	21	0	1	0	0	1	0	2
19	M	61	0	0	0	0	0	1	1
20	F	66	1	1	0	0	0	0	1
21	F	65	0	0	1	0	0	0	1
22	M	31	1	0	1	0	0	1	1
23	M	58	0	0	1	0	0	0	1
24	F	57	0	0	1	0	0	1	1
25	M	39	0	0	1	0	0	0	1
26	F	59	1	0	0	0	0	0	0
27	M	66	0	0	0	0	0	0	0

CTCAE, Common Terminology Criteria for Adverse Events; F, female; M, male; TTFields, tumor treating field.
[a] Diagnostic status: 0, recurrent; 1, newly diagnosed.

Additionally, an indoor temperature maintained at 22–24 °C and humidity controlled at 50%–60% reduces scalp sweating. Six patients who were capable of self-care were instructed to avoid high-intensity physical activities and exposure to sunlight, indoor air conditioning, and excessively hot environments, and to use two portable electric fans that provided ventilation to the array area to control scalp temperature and reduce the risk of hyperthermia and fever. The patients experienced a notable loosening of the transducer array on day 3, which was managed by reducing the interval until transducer replacement to 2 days. In addition to the above-described measures, the transducer array was appropriately reinforced with medical adhesive tape and for 1 patient with oily skin, an elastic head cover (which was separated from the scalp by a space of approximately 1–2 fingers' width) enhanced attachment (Fig. 1A). For one patient with limited mobility who was unable to move in the bed, the caregiver was instructed to help the patient to turn over frequently in order to avoid staying in the same position for longer than 2 h. Pressure sores—especially on the post-occipital region—and the melting of the hydrogel disks were prevented by placing a cushion in the helmet. Finally, a significant reduction in scalp sweating and improved adhesion of transducer array were observed in all eight patients after these adjustments, with little effect on the administration of TTFields therapy (Fig. 1B).

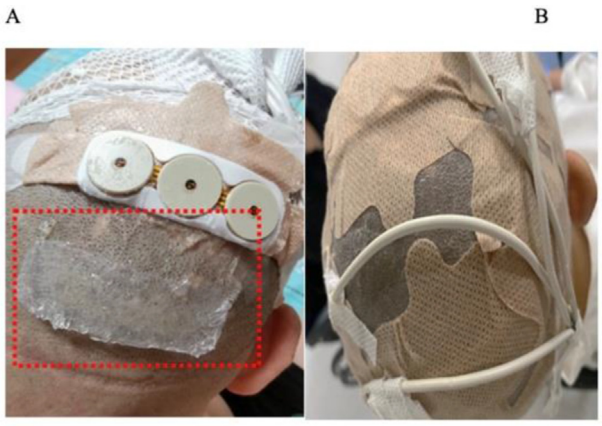

Fig. 1. (A) scalp sweating and the melting of the hydrogel disks before the management of hyperhidrosis, **(B)** the improved adhesion of transducer array after the management of hyperhidrosis.

Case 2 – Contact dermatitis

A total of 13 patients experienced a combination of at least one of the following symptoms after 1 day to 2 weeks of treatment: erythema, rash, blisters, and scalp itching. After laboratory testing, allergic contact dermatitis was diagnosed in six patients (46.2%), while seven patients (53.8%) with sensitivity to medical adhesive tape or hydrogel were diagnosed with irritant contact dermatitis.

Removing of the transducer array from the stimulation site, applying and maintaining 0.05% betamethasone gel to the affected scalp area for 3–4 h, and avoiding scratching were recommended to 11 patients who complained that pruritus had a major effect on sleep and/or daily activities. Following scalp washing with anti-seborrheic dermatitis shampoo marketed for babies, anerdian was used to disinfect the pruritus site before reapplying the transducer array. After 10 min to 1 day of this treatment, the pruritus resolved in most patients.

One patient reported erythema and patches of rash with scalp pruritus on the first day. Before the replacement of the transducer array, 0.05% zinc oxide ointment was continuously applied to the affected area until symptoms improved. However, erythema and rash recurred in the array area, suggesting sensitivity to the hydrogel or transducer array. In addition to a trimmed array, topical 0.05% clobetasol ointment was applied to the area of dermatitis accompanied by anti-allergic drug treatment before hair washing with Chinese medicine (ie. honeysuckle water, which is typically used for skin symptoms such as flushing, papules, and blisters without exudate[21]). The erythema and rash largely resolved over 3 days (Fig. 2).

Desquamating rash was dismissed by one patient, leading to blistering after 1 month of continuous TTFields therapy. Cold and wet compresses

Fig. 2. (**A**) One patient presented with erythema and rash in the array area before the management of Contact dermatitis, (**B**) the scalp appearance after the management of hyperhidrosis.

were applied for 30 min three times a day, and dexamethasone acetate cream was applied once daily to the blister without breaking it and a trimmed (more gas-permeable) array was applied. The blister started to resolve after 5 days with complete resolution after 8 days (Fig. 3).

Case 3 – Skin erosion and ulceration

A patient who was chronically bedridden developed a clinically symptomatic ulcer with a size of 10.0 × 4.0 mm (length × width) with white exudate during month 4 of TTFields therapy. Room temperature sterile physiological saline was used to clean the ulcer after discontinuing the TTFields therapy and chemotherapy. After twice-daily sterilization with anerdian, topical mupirocin ointment was applied. A dressing that promotes moist healing (eg. hydrocolloid) and can reduce gliosis between the dressing and newly formed granulation tissue was applied to prevent the aggravation of the injury.[22] It was important to reinforce instructions on the removal and placement of the transducer array to bedridden patients and their caregivers. To promote wound healing, the patient was instructed to take multivitamins and adopt a diet that was high in protein and cellulose and low in cholesterol (eg. fresh vegetables, fish, and eggs). With the resumption of TTF therapy, the scalp condition was regularly assessed. A blister machine that transforms shampoo into bubbly foam was useful for reducing friction on the scalp when shaving. The replacement transducer array was placed at least 2 cm from the skin ulcer until the wound was healed. The patient was re-treated with TTFields therapy when the skin ulcer became crusted, and the scab exuviated and healed naturally after 4 weeks (Fig. 4).

Case 4 – SSTIs

On day 4 of TTFields therapy, one patient presented with folliculitis and desquamation was observed at the site starting on day 12. The patient developed a herpes lesion (0.5 cm in diameter) with redness and a small amount of purulent discharge on the scalp. The cessation of TTFields therapy and chemoradiotherapy was recommended and pretreatment assessment with bacterial cultures and susceptibility testing were performed to identify pathogenic microorganisms and select targeted antibiotics. Topical mupirocin ointment was applied for 15 min following a thermal compress with saline gauze, while neomycin-containing ointment was generally not recommended. The transducer array was replaced after removing residual ointment at non-herpes lesion sites with anerdian. The patient and caregiver were instructed on the appropriate method of transducer array removal and replacement and the precautions that were needed, with emphasis on the importance of regular scalp assessment. The transducer array and adhesive residue from the previous transducer array were removed at an angle of 0° or 180° using mineral oil swabs. Wound healing was observed 2 weeks later with complete healing at the time of discharge (Fig. 5).

Case 5 – Xerosis or pruritus

Four patients had dry flaking skin, moderate pruritus, and dandruff. Topical skin care lotion or face cream rather than anti-dandruff or fragrance-containing shampoos were recommended. For pruritus, application of gentle pressure to the scalp with the fingers combined with topical corticosteroids and oral gabapentin was advised instead of scratching. Regular observation and frequent clinical assessment were also encouraged. The patients experienced symptom relief except for one patient with severe pruritus on the scalp who rejected the above recommendations and discontinued TTFields therapy (Fig. 6).

Discussion

There have been few advances in the treatment of GBM over the last four decades. TTFields therapy is a promising treatment that is considered as the fourth anti-cancer therapy along with surgery, chemotherapy, and radiotherapy. However, in order to maximize the clinical benefit of TTFields therapy, it is essential to manage dAEs.

Hyperhidrosis—a common TTFields-associated dAEs—is caused by multiple factors including climate, physical activity, concomitant

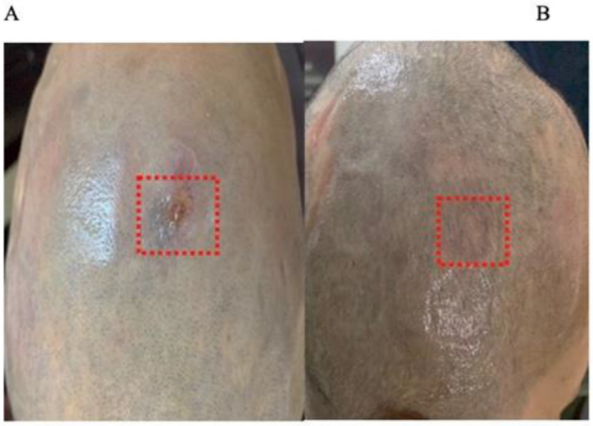

Fig. 3. (**A**) A blister of one patient with GBM before the management of contact dermatitis, (**B**) the scalp appearance after the management of hyperhidrosis. GBM, glioblastoma multiforme.

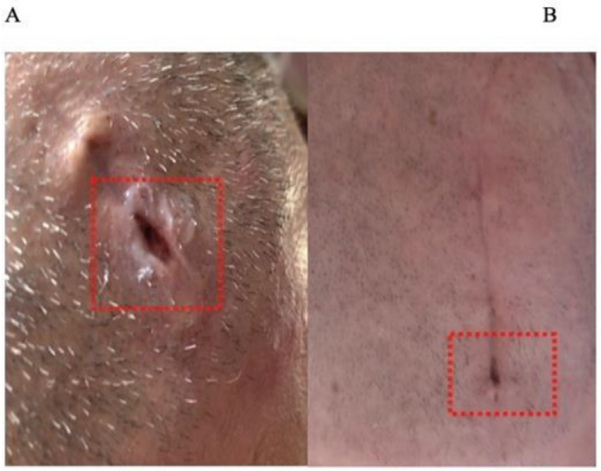

Fig. 4. (**A**) An ulcer with white exudate of one patient with GBM before the management of skin ulceration, (**B**) the scalp appearance after the management of skin ulceration. GBM, glioblastoma multiforme.

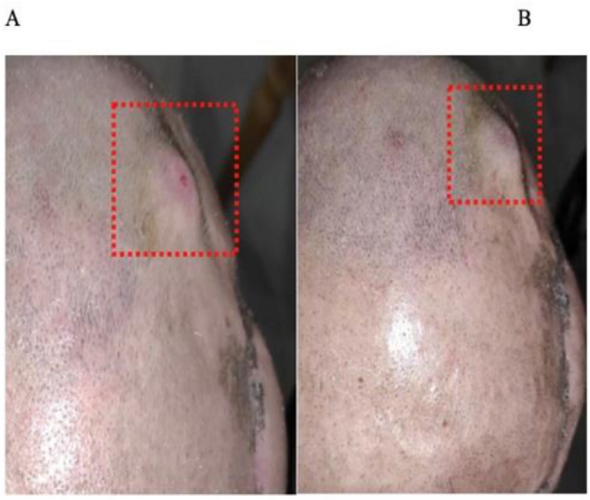

Fig. 5. (**A**) A herpes lesion of one patient with GBM before the management of skin and soft tissue infection, (**B**) the scalp appearance after the management of skin and soft tissue infection. GBM, glioblastoma multiforme.

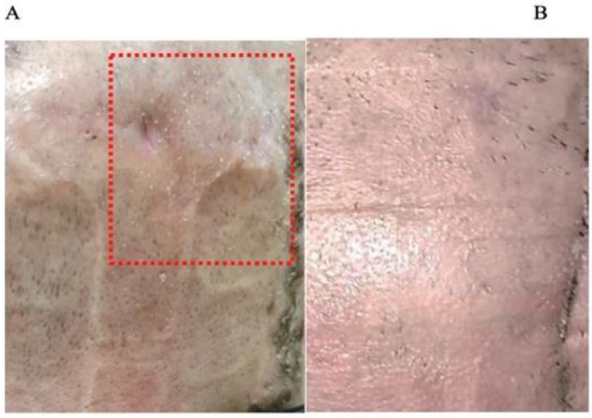

Fig. 6. (**A**) The xerosis of one GBM patient before managing, (**B**) the scalp appearance after the management of xerosis. GBM, glioblastoma multiforme.

medication, and genetic susceptibility.[12] The hydrogel disks in the transducer array are hydrophilic and susceptible to liquefaction in hot and humid climates or after intense physical activity.[23] All 8 patients (29.6%) presenting with hyperhidrosis resided in the subtropical region of China where they were exposed to high temperatures (up to 38 °C) as well as a high humidity level (~80%) year round.[24] Current treatment approaches for hyperhidrosis are limited to topical antiperspirants and glycopyrrolate. In this study, we developed a targeted, individualized management strategy for hyperhidrosis according to the underlying cause.

Contact dermatitis for patients undergoing TTFields therapy can be classified as irritant and allergic type caused by chemical irritants (eg. medical adhesive tape and hydrogels) and environmental allergens, respectively.[19] Previous studies have recommended the removal of the irritant or allergen from the area of dermatitis and application of T-type corticosteroids (eg. betamethasone, clobetasol, fluocinolone). For patients with high sensitivity to adhesive medical tape, the tape was trammeled and a wet compress was applied for 20 min three times a day until the dermatitis resolved.[12]

Skin ulcers are caused by local and systemic factors, and pressure ulcers are observed in up to 5% of hospitalized patients.[25] Superficial skin erosion is categorized as epidermal exfoliation caused by medications, skin erosion secondary to acute and chronic eczema, and acute and chronic wounds due to inadequate and inappropriate treatment,[26] which require different management strategies. There were no patients presenting with skin erosion in this study.

A substantial number of pathogenic microbes are present on the skin surface and in skin layers and supporting structures that can cause SSTIs when the skin barrier is damaged.[27] There is a high risk of SSTIs with a daily replacement and inappropriate removal of the transducer array. Moreover, TTFields therapy combined with other chemotherapy agents—especially anti-angiogenic medications—can increase the risk of dAEs.[12,17] Compared to previous studies, caregiver education was enhanced for our patients to aid in the timely resolution of SSTIs.

Xerosis has multiple causes, such as pharmacotherapy, genetic susceptibility, and a humid and cold climate, among others. The decreased cell proliferation and aberrant initiation of meiosis in the stratum corneum lead to thinning of the epidermis. Moreover, xerosis is often accompanied by pruritus due to dilated capillaries, increased histamine level and inflammation, and abnormal shedding of parakeratosis areas.[28] There are few targeted treatments for xerosis, and topical moisturizers and skin care to keep the affected area well moisturized are the management strategies recommended by evidence-based guidelines and expert consensus, although these have limited efficacy.[29] The resolution of xerosis in our patients was likely attributable to timely diagnosis and just-in-time intervention.

Although the dAEs in our patients were usually grade 1 or 2, a number of studies have shown that dAEs affect not only HRQoL but also the therapeutic efficacy of TTFields therapy, with some patients who are unable to tolerate severe rash discontinuing their treatment.[30,31] In this study, the transducer array was replaced daily for two patients; one of the patients developed SSTI during chemoradiotherapy and temporarily discontinued TTFields therapy. The simultaneous use of TTFields therapy and chemoradiotherapy can increase dAEs, so we recommend strengthening patients' and caregiver's education on dAEs risk, management, and prevention. Although there is no standardized approach for the treatment of dAEs associated with TTFields therapy, healthcare providers can still use the modified CTCAE to classify clinical symptoms for appropriate selection of antibiotics, moisturizing lotions, antihistamines, or steroid-based drugs as treatments.

This study summarized the targeted management of dAEs related to TTFields therapy (seen in Supplementary Appendix) based on real-world experience. Our findings can help healthcare providers and caregivers identify dAEs and provide treatment for hyperhidrosis, contact dermatitis, skin erosion and ulceration, SSTIs, xerosis, and pruritus. The strategies described herein achieved good results in all 27 patients with GBM undergoing TTFields therapy in the present case series. At the time of data cutoff, exacerbation of GBM resulted in the death of 10 patients; their caregivers indicated that the patients were unaffected by dAEs in the terminal stage of GBM after receiving the above-described treatments. The remaining patients continued TTFields therapy, except one patient who experienced severe pruritus and discontinued the treatment.

Limitations

This study had some limitations including a small number of cases, short follow-up time, and insufficient emphasis on patients' self-perceptions of HRQoL. Randomized controlled trials on the HRQoL of patients with GBM undergoing TTFields therapy with dAEs management are needed. Moreover, our results demonstrate that the incidence of TTFields therapy-associated dAEs is much higher than previously reported in the literature, although we did not identify the contributing factors. Additional studies are required to develop evidence-based guidelines for dAEs management that will enhance the clinical benefit of TTFields therapy.

Conclusions

An individualised care protocol for TTFields-related dAEs that can improve HRQoL and treatment adherence and efficacy can be developed

by healthcare providers based on the findings and recommendations of this study.

Data on TTFields-related dAEs is rarely reported, and published reports of management of scalp dAEs are lacking. This case series summarizes a clinically individualized management for TTFields-related dAEs.

Ethics statement

This study had been approved by the Ethics committee of State Key Laboratory of Oncology in South China on April 30, 2020 (B2020-051), and all patients filled in informed consent form and showed their agreement to participate this study.

Consent for publication

Then consents to publish individual images were obtained from all patients.

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Nil.

Authors' contributions

All authors contributed to the conception, design, coordination and drafting of the manuscript. All authors read and approved the final manuscript.

Declaration of competing interest

None declared.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.apjon.2022.100095.

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